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Modeling the cost-effectiveness of strategies for treating esophageal adenocarcinoma and high grade dysplasia

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Abstract

Objective: To synthesize cost and health outcomes for current treatment pathways for esophageal adenocarcinoma and high grade dysplasia, and model comparative net clinical and economic benefits of alternative management scenarios.

Methods: A decision-analytic model of real-world practices for esophageal adenocarcinoma treatment by tumor stage was constructed and validated. The model synthesized treatment probabilities, survival, quality-of-life and resource use extracted from epidemiological datasets, published literature and expert opinion. Comparative analyses between current practice and five hypothetical scenarios for modified treatment were undertaken.

Results: Over five years, outcomes across T stage ranged from 4.06 quality-adjusted life-years and costs of $3,179 for high grade dysplasia, to 1.62 and $50,226 for stage T4. Greater use of endoscopic mucosal resection for stage T1 and measures to reduce esophagectomy mortality to 0-3% produced modest gains whereas a 20% reduction in the proportion of patients presenting at stage T3 produced large incremental net benefits of $4,971 (95% interval: $1,560, $8,368).

Conclusion: These findings support measures that promote earlier diagnosis, such as developing risk assessment processes or endoscopic surveillance of Barrett's esophagus. Incremental net monetary benefits for other strategies are relatively small in comparison to predicted gains from early detection strategies.

Key words: adenocarcinoma of the esophagus, endoscopic mucosal resection, decision-analytic model

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Introduction

Esophagectomy is currently the standard surgical treatment for esophageal adenocarcinoma. However, only 25-35% of patients presenting with this disease actually undergo surgery, either due to metastatic disease, or comorbidities. New endoscopic techniques such as endoscopic mucosal resection (EMR) offer a new approach for early stage disease. EMR can be used to assess the depth of tumor invasion, and in some cases it is definitive treatment. Further, the combination of EMR and radiofrequency ablation (RFA) is emerging as an option for more diffuse intra-mucosal disease[1],[2-4].

Few studies have assessed the cost-effectiveness of treatments for esophageal cancer and high grade dysplasia. Pohl *et al.* 2009 assessed the cost-effectiveness of combination EMR/RFA in patients with stage T1a esophageal adenocarcinoma, and suggested that RFA was cost-effective over a 5-year time frame[1]. Similarly, a UK study by Boger *et al.* 2010 compared first-line RFA (with esophagectomy for subsequent recurrence/progression) versus esophagectomy in patients with high grade dysplasia, and although modeling was limited to two years follow-up, they concluded that RFA was a cost-effective option.

Studies have produced mixed results for benefits for early cancer detection in Barrett's esophagus surveillance programs[5]. To date, there is a lack of evidence on crucial data estimates (e.g., quality of life, proportion of patients progressing from low- to high-grade dysplasia), and analyses have not adequately scrutinized the clinical uncertainty of alternative management options[5]. Compared with other gastrointestinal cancers, there is limited evidence about the cost and health impact of new or modified strategies for controlling esophageal adenocarcinoma. These include substituting esophagectomy with endoscopic therapies (EMR/RFA), or chemoradiotherapy, concentrating surgical work to high-volume

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centers, and early testing of tumor response during neoadjuvant chemotherapy by PET scan with subsequent targeted care.

To address questions of cost-effectiveness, it is necessary to understand the baseline health resource use and outcomes for treating esophageal adenocarcinoma or high grade dysplasia in a way that reflects real-world practice [6]. An overview of the major practice patterns, natural history and management of esophageal cancer and the associated health care resources used in a large Australian patient cohort (n=1100) has been reported recently [6]. To better evaluate the current range of treatment options, we examined treatment pathways and outcomes for esophageal adenocarcinoma, as well as Barrett's esophagus with high grade dysplasia. Patient survival, health-related quality of life and associated events, resource use from associated treatments, and cost were estimated for current management pathways, and a decision-analytic health economic model was developed. Alternative hypothetical management scenarios were then compared to current pathways to estimate potential benefits for alternative scenarios and management strategies.

Materials and Methods

Model structure

A decision-analytic model was constructed in TreeAge Pro 2011 software (TreeAge Software Inc, Williamstown, MA, USA) (Figures 1a and 1b). This model explicitly identified the sequence and linkage of the major treatment pathways for different stages (T1-4) of esophageal adenocarcinoma, and also for high-grade dysplasia (HGD) in Barrett's esophagus, and tracked cohorts of patients with these diagnoses. To allow the majority of resource use and survival outcomes to accrue, the time horizon extended to five years after diagnosis. To

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ensure that the model reproduced real-world practice, the medical pathways were identified and independently confirmed by five specialist upper gastrointestinal surgeons who were all actively engaged in esophageal cancer management. Several iterations of the model were constructed before the model was finalized, with consensus reached when it was necessary to balance treatment complexity with data availability.

The model pathways were first divided into T stages (i.e., American Joint Committee for Cancer tumor stages T1 to T4) at diagnosis, and separate pathways were also constructed for patients with distant metastases, and patients presenting with HGD. Pathways for stages T2 to T4 were structurally identical, with patients receiving either non-surgical treatment or surgical treatment, with or without neoadjuvant therapies (Figure 1b), although the probabilities of different outcomes differed according to clinical stage. Those undergoing surgical treatment (with or without neoadjuvant therapy) followed paths where they either died peri-operatively, died after tumor recurrence with distant metastases, died after a period of time from unrelated causes, or remained alive with no tumor recurrence at five years. Pathways for T1 stage and HGD were more complex (Figure 1a), and also included endoscopic ablation of Barrett's esophagus and endoscopic mucosal resection options, either alone or prior to tumor recurrence and subsequent esophagectomy. The model allocated patients to stages and associated treatment pathways according to mutually exclusive probabilities (Table 1). Health outcomes and costs were assigned to the terminal node of each pathway and values were calculated for each course of action along the decision tree[7].

Data sources

The main types of data in the model were treatment probabilities, survival (years), utilities (i.e., preference-based health-related quality of life) and medical costs. Data used to populate

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the model were based where feasible on the Australian Cancer Study Clinical Follow Up (ACS), a 'patterns of care' study which included 795 patients with esophageal adenocarcinoma or gastro-esophageal junction adenocarcinomas. These patients were recruited between 2002-2008, had a mean age of 62 years, 61% were men, predominantly Caucasian, and 25% were current smokers[8]. ACS data were supplemented with data from prospectively collected datasets stored in databases and maintained by the major esophageal cancer units in Adelaide and Brisbane, Australia. These data sets contained outcome data from more than 2000 individuals with esophageal cancer, and more than 1000 patients who had undergone an esophagectomy. Other treatment probabilities were determined from review of published literature and Australian all-cause mortality data (Table 1). Odds ratios were applied to baseline risk to consistently model treatment effects on absolute incremental survival[9] .

As the ACS included only patients with invasive esophageal adenocarcinoma, we reviewed the literature (see Appendix 1 for search terms) to obtain treatment estimates for patients presenting with high-grade dysplasia, and then checked these data for consistency against the prospective database maintained in Adelaide, South Australia. Remaining gaps in evidence to populate the decision tree were derived from consensus views of the five surgeons (expert opinion) (see Appendix 2).

Costs of treatment were calculated from patient-level resource data collected by the ACS over several years via medical chart review[6]. Prices applied to resource use were taken from national price schedules and public hospital clinical costings for inpatient surgical stays. The mean cost of an esophagectomy included in-hospital adverse events, and intensive care unit admissions for some patients[6]. Statistical analyses of costs allowed for their skewed

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nature [10]. Australian life-tables provided information on background all-cause mortality[11]. Utility scores to adjust survival estimates in estimating quality-adjusted life years were obtained from a literature review on utility weights for treatments for esophageal adenocarcinoma[12-15]. Table 1 lists all data estimates and tabled data in the model with their respective sources and ranges tested in sensitivity analyses (see below). In addition, based on ACS and Adelaide datasets, treatment probabilities for neoadjuvant therapy plus surgery across tumor stages ranged from 0.62 (T2) to 0.81 (T4), 0.71 to 0.77 for surgery without neoadjuvant therapy, 0.02 to 0.06 for peri-operative deaths, 0.19 to 0.42 for being alive at five years following surgical treatment, and 0.26 to 0.48 for being alive at five years following neoadjuvant with surgical therapy.

Analyses

Using a natural history model with current practice, we estimated the economic outcomes for treatment options connected with actual patterns of care for managing patients with a diagnosis of HGD or esophageal adenocarcinoma. Our analysis took an Australian health system perspective when measuring and valuing health care resources. Costs were valued in 2009 Australian dollars and converted to 2009 US dollars using a purchasing power parity of 1 AUD = 1.553 USD[16]. All dollars presented here are USD ($). Further details on the resource quantities and medical costs have been published previously[17]. Costs and quality-adjusted life years were discounted at 5% annually. The costs and effects of current practice were compared with the hypothetical scenarios described in Table 2 and incremental net monetary benefit (net benefit) generated. For comparing the current treatment with each hypothetical scenario separately, incremental net benefit was calculated over a 5-year period as:

$$\text{Incremental net benefit} = \lambda \times \Delta E - \Delta C$$

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where λ= \$50,000 was the base case threshold value applied to incremental quality-adjusted life-years gained (ΔE) and ΔC is the incremental cost. A decision-making threshold of \$50,000 was used. The strategy with the highest positive incremental net benefit (hereafter called 'net benefit') is the preferred option, whereas a negative net benefit indicates a net loss and such a strategy should not be adopted.

Sensitivity analyses

Probabilistic sensitivity analyses on net benefit were undertaken to examine the joint variation possible within the data point estimates used in the model, based on their known distributions. Beta distributions assigned to treatment probabilities, *Dirichlet* distributions for dependent variables (e.g., proportions in each T stage), log normal distributions to survival estimates and gamma distributions to cost variables because costs were right-skewed[6] (Table 1). Where patient-level data were used (e.g., from the ACS) the distributions assigned were based on means, standard deviations and medians, where appropriate. The analyses were conducted by re-sampling from the nominated parameter distributions across 5,000 iterations (Monte Carlo simulation). Simulated mean net benefits with 95% uncertainty intervals (95%UI) were generated to estimate the extent of uncertainty for each comparison.

Alternative management scenarios

To evaluate the impact of changing clinical practice and outcomes, five hypothetical scenarios were tested. These involved changing current therapy by:

(1) Altering the proportion of patients with stage T1 adenocarcinoma undergoing endoscopic mucosal resection;
(2) Modifying peri-operative mortality rates for esophagectomy;
(3) Increasing the proportion of patients diagnosed at earlier stages;

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(4) In patients undergoing neoadjuvant chemotherapy, adding fluorodeoxyglucose positron emission tomography after the first cycle of chemotherapy to assess tumor response, and modify treatment to progress directly to surgery if poor response; and
(5) Increasing the proportion of patients undergoing definitive chemoradiotherapy as first-line therapy.

Full details and the rationale behind each of the five scenarios are given in Table 2.

Results

Over five years, the total medical cost for treating an individual with esophageal adenocarcinoma varied between $33,572 and $50,226, depending on T stage (Table 3). Costs were $8,267 for patients with distant metastases. Over five years, survival ranged from 0.97 to 4.66 years with a mean 2.5 years for T stages T2 and T3. Patients with HGD incurred fewer costs ($23,179) than patients with invasive adenocarcinoma, and had a mean survival of 4.6 years over five years of follow up. Overall, current treatment patterns for HGD and adenocarcinoma of the esophagus had mean quality-adjusted life years of 2.25 and mean costs of $41,345 over five years (Table 3).

Compared with current treatment costs and outcomes for HGD and esophageal adenocarcinoma, the greatest additional net benefit per patient among the five scenarios of interest was observed for potentially down-staging T3 tumors through earlier detection (Table 4). The incremental net benefit was $4971 (95%UI: $1560, $8368) for a 20% reduction in the proportion of patients presenting with stage T3 disease, redistributed equally to T2, T1 and HGD (Table 4), corresponding to modest gains from a hypothetical early detection process. Net benefits were relatively modest but positive (cost-effective) for a peri-operative mortality rate of 1% (net benefit $233, 95%UI: -$297, $95), increased use of EMR treatment in patients with T1 stage adenocarcinoma (e.g., 100% T1a + 25% T1b: net benefit $428,

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95%UI: $182, $726) and adding fluorodeoxyglucose positron emission tomography for assessing response to neoadjuvant therapy (net benefit $805, 95%UI: $59, $1596), and increasing the use of chemoradiotherapy in T2 and T3 by 25% (net benefit $2660, 95%UI: -$1716, $9712)(Table 4). Net benefits were positive but inconclusive for the use of chemoradiotherapy as definitive treatment for T2 and T3 cancers (replacing esophagectomy as definitive treatment) indicated by the 95% limits spanning across expected net loss to net benefit (Table 4).

Discussion

Cost-effectiveness analysis is the process of systematically comparing the relative health care costs and benefits of alternative strategies to inform decision-makers of the strategy or treatment pathways with highest net benefit [18], as well as those likely to provide better value if implemented more widely, and areas which might benefit from further research [19-21]. Systematic assessment of incremental costs and effects requires consideration of natural history and interaction with practice, and this is particularly important for conditions such as esophageal adenocarcinoma which has multiple strategies and pathways for monitoring, diagnosis and management, all conditional on the stage of disease at presentation[22]. While costs might be of secondary concern to clinicians who primarily seek to optimize outcomes for individual patients, ultimately, resource allocation decisions do affect everyday clinical care in settings with budgetary pressures [23]. It is mandatory for regulatory bodies in Canada, UK, Australia and most of the Western world to evaluate cost-effectiveness of new technologies when considering potential government reimbursement.

Our results suggest that compared with current practice, potential incremental net benefit, at a threshold value of $50,000 per quality-adjusted life year, is greatest for early detection in the

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context of a Barrett's esophagus surveillance program which shifts the proportion of patients presenting with stage T3 cancer to earlier stages (e.g., $4971 with 20% down shift in T3). This is due to this strategy having a marked impact on both increased survival prospects and lower costs associated with treatment pathways for patients with stage T1 adenocarcinoma or HGD. However, the cost to implement early detection strategies (e.g., surveillance, detection through biomarker screening) is not included in the net benefit results, and will have the impact of lowering this net benefit. Further modeling will be required to evaluate this further, and our model suggests that the cost of early detection strategies which down stage 20% of individuals with T3 stage to HGD or T1, must not exceed $4971 per patient within the early detection program for it to be a worthwhile health care investment.

Since there are currently only a small proportion of patients presenting with stage T1 adenocarcinoma (15.2%) or HGD (2.2%) relative to stage T2-T4 adenocarcinoma, the economic impact of strategies which only improve the outcome for early stages, but not increase the proportion presenting with early stage disease, is likely to be quite modest when evaluated in the context of the overall population. On the other hand strategies that increase the proportion with early stage disease, by shifting people from late stage to early stage might be more promising, and do not depend on the development of new technologies or devices. This was shown in our findings when, for example, where hypothetically an increased proportion of patients with stage T1 adenocarcinoma underwent EMR rather than esophagectomy produced a net benefit of only $428, a much smaller gain than for early detection strategies. Despite this, our results support the use of EMR for T1 tumor treatment as shown by the positive net benefit. This result is also consistent with previous health economic reports of endoscopic techniques as preferred treatments for HGD and stage T1 adenocarcinoma versus esophagectomy [24-25].

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Utility scores following esophagectomy over the longer-term and the cost for esophagectomy were critical parameters in our natural history model. The high cost of the hospital episode for esophagectomy is also reflected in the analyses. Surgical treatment is complex, and it is common for adverse events to occur, resulting in lengthy hospital stays and longer recovery periods in some patients. Previous work on patient-level resource data, that formed the basis of the cost estimates modeled here, showed that that 24% of the patients undergoing esophagectomy experienced at least one significant complication and the mean length of stay for the surgical episode was 15.5 days [6]. Many of the patients undergoing esophagectomy were hospitalized for a much longer period of time [6], whereas radiofrequency ablation and EMR are typically same-day procedures. However, these endoscopic procedures usually require several procedures per patient to complete a course of treatment [1]. In assessing the subset of patients specifically with stage T1 adenocarcinoma or HGD, our results suggest that some economic efficiency might be gained from treatment pathways which involve less-invasive endoscopic therapies. This is driven by reduced treatment related morbidity and mortality and lower costs compared to surgery.

In our study, hypothetically modelling different mortality rates for esophagectomy yielded different outcomes. When mortality rates were 5% or 10% there was no net benefit for the use of esophagectomy, although there was a benefit for mortality rates of 0%, 1% and 3%. This suggests that the perioperative rate for esophagectomy has a critical impact on whether or not this procedure is clinical effective and cost effective in patients with early stage disease, and it is likely that perioperative mortality rates of no more than 3% are required for esophagectomy to be an appropriate procedure for the treatment of these patients.

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Mortality associated with esophagectomy has progressively declined over recent decades. A review of esophagectomy outcomes for the 1990's showed a 8.8% in hospital mortality rate for this decade[26], although lower mortality (<5.0%) was observed in high volume centres [27]. More recent reports from the 2000's describe mortality rates of 3-5%, again with lower mortality rates consistently reported from high volume centres [28]. A study from our centres described an in hospital mortality rate for esophagectomy in five Australian hospitals of 3.5%[29]. A lower mortality rate of 1.2% has been reported for esophagectomy in patients specifically presenting with stage T1 adenocarcinoma or HGD[30]. Our current study supports surgical treatment for early stage esophageal cancer only in centres which can consistently achieve mortality rates for esophagectomy of 3% or less for patients with this disease stage.

Our study has a number of limitations. Despite the use of large Australian-based datasets, which reflect recent health care utilization and the natural history of esophageal adenocarcinoma, a number of gaps remained for uncommon pathway probabilities and it was necessary to depend on published reports or even clinical judgment for some of these. In part this occurred because ablation therapies are relatively new. The esophageal surgeons contributing to the development of this model all worked in high volume hospitals, and some also had personal experience with endoscopic ablative therapies. Whilst using "expert opinion" may have introduced some bias, this was counteracted by testing across a distribution of plausible values to address the potential uncertainty. Finally, utility scores, similar to health-related quality of life assessments, from Australian patients were unavailable and therefore we relied on those reported in the literature for US and European populations.

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The implications of our modeling lend support to measures that promote earlier presentation of tumors, such as developing risk factor assessment processes and endoscopic surveillance of Barrett's esophagus. This has been a particularly contentious topic with health economic studies producing mixed results as to the cost-effectiveness of endoscopic surveillance of Barrett's esophagus [5]. In 2009 two US studies recorded mean costs per patient under surveillance of $2,769[31] and $11,532[32] for surveillance programs involving 5-yearly screening intervals, and $7,940 was reported for one UK study with 3-yearly intervals (converted to $ 2009)[13]. Our cost cut-off of $4971 per patient within an early detection program appears to be in the overall range of these costs. However, research is still needed to explicitly model the long-term economic impact of surveillance of Barrett's esophagus, and this should incorporate natural history models for current treatment, intervention resources, screening intervals and adverse events.

There is widespread interest in improving health outcomes for patients with esophageal adenocarcinoma and in particular, diagnosing this disease at an earlier stage, so that less invasive endoscopic options such as mucosal ablation and endoscopic mucosal resection can be applied. The majority of patients currently present with stage T2-T4 tumors, and only a minority present with early cancer or HGD. Consequently, to improve outcomes the most promising cost-effective approach might be early detection to avoid esophagectomy, chemotherapy and radiotherapy. Our data suggest that this requires down-staging of at least 20% of T3 tumors to stage T1 or HGD, at a cost of less than $4971 per patient under surveillance.

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Appendix 1. Literature search terms for model probabilities
Database: PubMED, MEDLINE

For EMR (split between T1m T1sm) data:
(esophagus OR oesophagus) AND dysplasia AND (T1a OR T1s OR T1b or T1sm)
8 results. References from selected papers to be searched.

For ablation findings:
(esophagus OR oesophagus) AND (radiofrequency OR RFA) AND ablation AND (dysplasia OR HGD)
24 results. References from selected papers to be searched.

For surgical and endoscopic therapy survival or other data:
(esophagus OR oesophagus) AND (T1a OR T1s OR T1b or T1sm) AND (survival OR mortality)
12 results. References from selected papers to be searched.

Appendix 2. Method to elicit expert opinion for some data estimates

Independent interviews were undertaken between authors LG and NG and five esophageal surgeons. The interviews were designed to ask the same set of questions where gaps existed in the literature. Responses were recorded and the range of all responses collated. Consensus was reached via email correspondence after the surgeons were given the opportunity to agree/disagree with the group range. An average was taken of each estimate for the baseline model and range included in the sensitivity analyses. The surgeons were chosen from high-volume centres and with an active interest in esophageal cancer research. The locations spanned two Australian states and surgeons worked in private and public hospital settings.

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Table 1. Model data estimates with their distributions and sources.

Description	Base estimate (SD)	Distribution	Source
Costs (Mean AU$)			
Esophagectomy[1]	51,565 (36,749)	Gamma (α= 1.9689, λ<0.0001)	ACS[2]
Neo chemorad	25,732 (34,693)	Gamma (α= 0.5501, λ<0.0001)	ACS
Radiotherapy for pts treated surgically	5,782 (3,339)	Gamma (α= 2.9986, λ=0.0005)	ACS
Endoscopic mucosal resection (5 yrs)	12,134	Gamma (α=11.1123, λ=0.0009)	Ade[3]
Ablation (5 yrs)	17,419	Gamma (α= 11.1098, λ=0.0006)	Ade
Diagnostic tests for esophageal adenocarcinoma	2,338 (749)	Gamma (α=9.7437, λ=0.0042)	ACS
Follow-up in surgically treated pts	6,433 (4,059)	Gamma (α=2.5126, λ=0.0004)	ACS
Follow-up in non-surgically treated pts	11,524 (5,762)	Gamma (α=4.0003, λ=0.0004)	ACS
Palliative chemorad and stenting	10,500	Gamma (α=11.1111, λ=0.0011)	Ade
Definitive chemorad for pts not treated surgically	17,900	Gamma (α= 1.1111, λ=0.0006)	ACS
Definitive chemorad for pts treated surgically[4]	3,500	Gamma (α= 11.1111, λ=0.0032)	ACS
Probabilties[5]			
Pts in each T stage (T1-T4, DM)	0.022, 0.152, 0.228, 0.431, 0.052, 0.115	Dirichlet (25; 170; 255; 482; 58; 129)	ACS/ Ade[6]
Treatment for HGD (EMR, Ablation, no treatment)	0.85, 0.08, 0.07	Dirichlet (85, 8, 7)	Expert
Treatment for T1 (esophagectomy, EMR, Radiation, no treatment)	0.43, 0.47, 0.05, 0.05	Dirichlet (43, 47, 5, 5)	Expert
Recurrence after ablation for T1a/HGD	0.036	Beta (n=303, r=11)	Shaheen& Prasad
Recurrence after ablation has DM	0.182	Beta (n=11, r=2)	"
Alive[7] if HGD pt receives no treatment	0.600	Beta (n=100, r=60)	Expert
EMR of T1 will detect a T1a	0.784	Beta (α=9.6, β=2.6)	Peters 2005 & 2008
T1a receives ablation	0.400	Beta (n=100, r=40)	Expert
T1b pt eligible and receiving surgery	0.700	Beta (n=100, r=70)	Expert
Local recurrence after ablation receiving EMR	0.330	Beta (α=29.8, β=60.5)	Expert
Alive for recurrent local T1 receiving EMR	0.800	Beta (n=100, r=80)	Expert
T1b not receiving surgery will get radiation	0.722	Beta (n=18, r=13)	ACS
Alive for T1 receiving radiation only	0.125	Beta (n=32, r=4)	ACS/Ade
Alive after esophagectomy for T1 tumour	0.636	Beta (n=118, r=75)	"
T1 death from surgery	0.017	Beta (n=120, r=2)	"
Survival (mean, years)			
With DM	0.971	Log normal (μ=-0.234, σ=0.640)	ACS
For those dying peri-operatively	0.500	Beta (α=3.125, β= 3.125)	"
Survival for T1-2 cases receiving surg with neo	1.805	Log normal (μ=0.590, σ= 0.033)	"
For T1-T2 not receiving surgery	1.243	Log normal (μ=-0.118, σ=0.819)	"

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For T3-T4 cases receiving neo	1.622	Log normal (μ=0.347, σ=0.523)	"
For T3-T4 cases not receiving surgery	1.112	Log normal (μ=-0.170, σ=0.743)	"
For any T stage receiving surgery	1.753	Log normal (μ=0.401, σ=0.567)	"
Utilities (HRQoL score 0=poorest, 1=highest)			
Diagnosis of HGD	0.84	Beta (α=7.1111, β=1.3545)	[33,15]
Diagnosis of T1 or T2	0.838	Beta (α=7.2000, β=1.3919)	[13]
Diagnosis of T3 or T4	0.66	Beta (α=15.1111, β=7.7845)	[13,33]
Distant metastases	0.345	Beta (α=29.1111, β=55.2689)	[12]
Successful ablation	0.93	Beta (α=3.1111, β=0.2342)	[15]
Residual metastases/dysplasia after ablation	0.90	Beta (α=4.4444, β=0.4938)	[15]
Immediately following esophagectomy	0.86	Beta (α=6.2222, β=1.0129)	[12]
Long-term utility following esophagectomy	0.92	Beta (α=3.5556, β=0.3092)	[12]

Pts=patients, DM=distant metastases, Neo=neoadjuvant therapy, chemorad=chemoradiotherapy, HRQoL=Health-Related Quality of Life, HGD=high grade dysplasia, EMR=endoscopic mucosal resection

1. Includes the cost of post-operative tests and, for a proportion of patients, complications and subsequent longer hospital stay.
2. ACS: patient-level resource data from the Australian Cancer Study Clinical Follow Up [17]
3. Ade = Adelaide; Based on point estimates from dataset at Flinders Medical Centre and Royal Adelaide Hospital (n=325)
4. Includes patients who received or did not receive neoadjuvant therapy.
5. To conserve space, the probabilities for T2 to T4 are not provided in the table and are described in the main text.
6. Weighted average of Adelaide and ACS CFU datasets.
7. Alive is assumed to mean alive at 5-years from diagnosis

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Table 2. Description and rationale of five hypothetical scenarios tested

Scenario Name	Description	Rationale
EMR	Increasing the number of patients with stage T1 esophageal adenocarcinoma undergoing EMR, rather than esophagectomy (proportion of patients with T1a increased to 100% and then T1b additionally increased by 25%, 50%)	Growing evidence that EMR may produce clinically equivalent outcomes, fewer side-effects and quicker recovery compared with esophagectomy in patients with stage T1a esophageal adenocarcinoma.
Operative Mortality	Altering peri-operative mortality rates for esophagectomy to 1%, 3%, 5%, 10% (applied to all T stages)	Average rate of 3.7% seen in NSW[34], rates differ by high vs. low volume hospitals, 1% mortality in patients undergoing esophagectomy for surveillance detected early stage cancer.
Downstaging	Increasing the numbers of patients diagnosed at T2, T1 and HGD stages by assuming a proportion of patients with T3 tumours are absorbed equally across the T2, T1 and HGD categories. Proportions included 10%, 20%, 30%, 40%	As more patients with Barrett's esophagus are monitored through endoscopy surveillance programs, increasing numbers of cancers are expected to be detected at earlier T stages. The value of INB here corresponds to the maximum per patient cost of a cost-effective surveillance program with associated level of effectiveness
Add PET	Adding FDG-PET to T2 and T3 pathways after first cycle of neoadjuvant chemotherapy to aid identify poor responders. Poor responders then discontinue neoadjuvant therapy. Assumed 64% responders [35].	If FDG-PET is successful in accurately differentiating responders vs. non-responders, therapy can be more effectively targeted, and can avoid unnecessary neoadjuvant therapy in likely non-responders.
Chemo/radiotherapy	Increasing the proportion of patients with T2 and T3 stage cancer receiving definitive chemoradiotherapy (replacing esophagectomy) and receive esophagectomy for recurrent cancer. Proportions included 25%, 50%, 100%	Anecdotal evidence that some patients respond as well to definitive chemoradiotherapy as they do to surgery.

EMR = endoscopic mucosal resection, NSW=New South Wales, RCT=randomized controlled trial, DM=distant metastases, Neo=neoadjuvant therapy, chemorad=chemoradiotherapy, QALYs= Quality-Adjusted Life Years, HGD=high grade dysplasia, EMR=endoscopic mucosal resection, Chemo=chemotherapy, FDG-PET = fluorodeoxyglucose positron emission tomography

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Table 3. Natural history cost, life years and QALYs over 5 year follow up with current practice by HGD and cancer T stage (means)

Stage	Costs (USD)	Life years	QALYs
HGD	23,179	4.55	4.06
T1	33,572	4.66	4.26
T2	50,377	2.53	2.18
T3	50,001	2.51	2.07
T4	50,226	2.03	1.62
Distant metastases	8,267	0.97	0.33
Total	41,345	2.69	2.25

HGD = high grade dysplasia, QALYs = quality-adjusted life years

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Table 4. Incremental net benefits for specified scenarios in relation to the base case (USD)

	Base value	New value	Inc[1] Costs $	Inc[1] QALYs	Inc net benefit[1] $ (95% UI)
EMR for T1[2]	T1a 90% EMR/Ablat T1sm 70% Esophag, 0%EMR/Ablat				
1. 100% T1a		100% T1a	-256	-0.001	228 (43, 477)
2. 100% T1a +25% T1b		100% T1a +25% T1b	-357	0.002	428 (183, 726)
3. 100% T1a +50% T1b		100% T1a +50% T1b	-458	0.005	628 (296, 1018)
Operative Mortality	2% to 6% depending on T stage				
1. 0%[3]		0%[3]	225	0.049	1367 (798, 2166)
2. 1%		1%	166	0.036	989 (455, 1726)
3. 3%		3%	8	0.001	233 (-297, 895)
4. 5%		5%	-70	-0.018	-523 (-1133, 113)
5. 10%		10%	-364	-0.086	-2413 (-3455, -1593)
Down staging T3	n(T3)=482[4]				
1. 10%		n(T3)=434	-531	0.061	2468 (-480, 5497)
2. 20%		n(T3)=386	-1065	0.124	4971 (1560, 8368)
3. 30%		n(T3)=337	-1598	0.185	7490 (3420, 11363)
4. 40%		n(T3)=289	-2128	0.248	9975 (5287, 14243)
Add PET 64% respond to neoadj chemorad (Total within T2 and T3)	$16,569	Cost chemorad[5] (T2)=$14,958 (T3)=$13,437	-833	0.000	805 (59, 1596)
Chemorad	Esophag 1st line n(T2,T3)=196, 362	Chemorad 1st line[2]:			
1. 25%		n(T2,T3)=49, 91	-842	0.056	2660 (-1716, 9712)
2. 50%		n(T2,T3)=98, 181	-1683	0.113	5323 (-3432, 9424)
3. 100%		n(T2,T3)=196, 362	-3366	0.226	10641 (-6864, 38848)

1. Probabilistic sensitivity analysis using 5000 Monte Carlo simulations. Net monetary benefit at a threshold value of $50,000 per QALYs. UI- uncertainty interval, 2.5% and 97.5% ranked values after sorting min to max. Incremental net benefits using current practice (see table 3) as the reference case for each scenario.
2. Replaces esophagectomy, outcomes remain the same for esophagectomy
3. New %peri-op mortality rate applies to all T stages
4. Dispersion into earlier stages not shown in new value column. Baseline values for numbers of patients are:T3=482, T2=255, T1=170, HGD=25
5. Based on formula cost(T2)=($25732 +$928)*0.80 + ($8577 + $928)*0.20, cost(T3)= ($25732 +$928)*0.62 + ($8577 + $928)*0.48. $8577 of chemrad costs is incurred for 2 weeks treatment before a response is known/tested for.

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Figure 1a Illustration of decision-analytic model for T1 and HGD

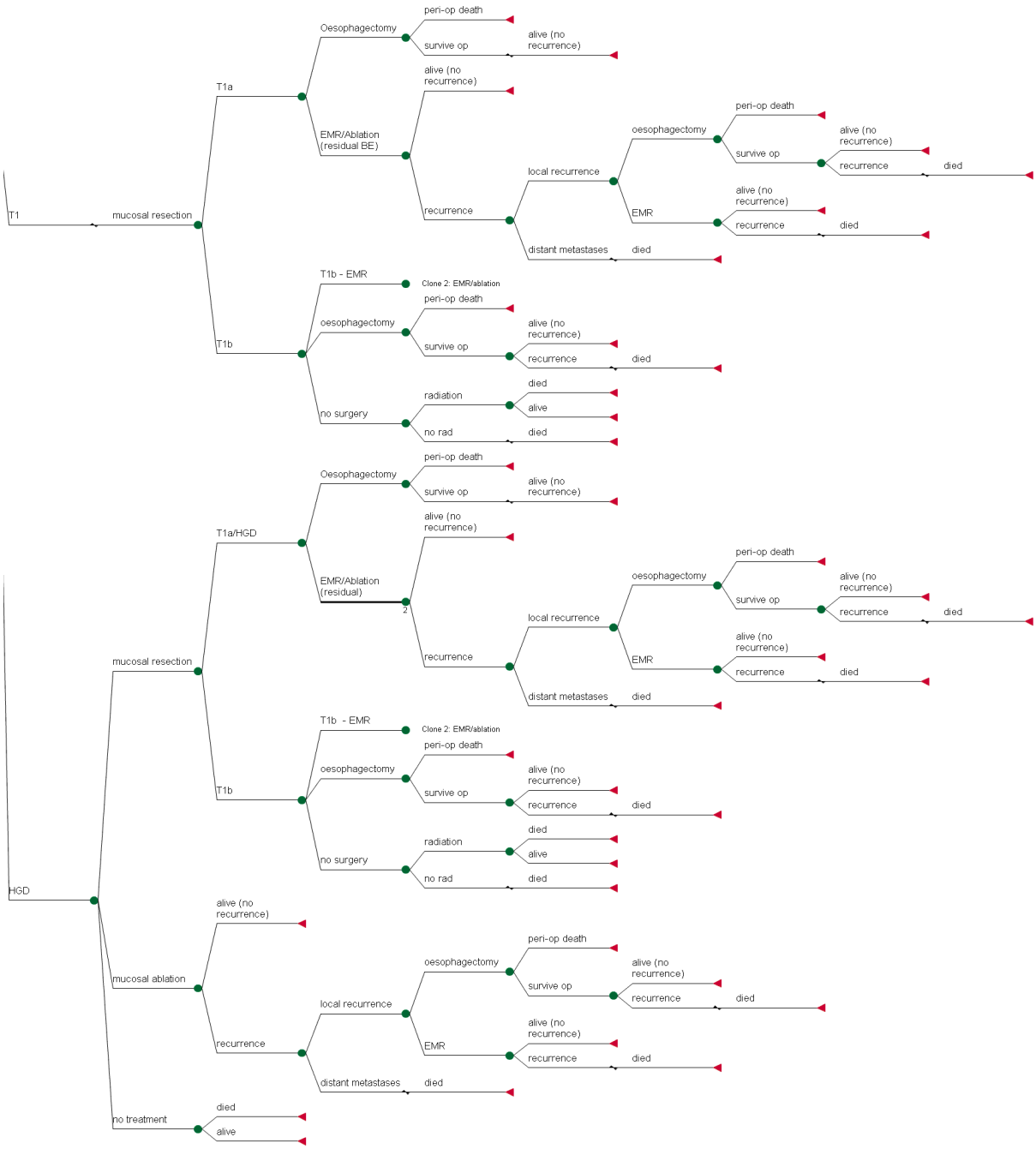

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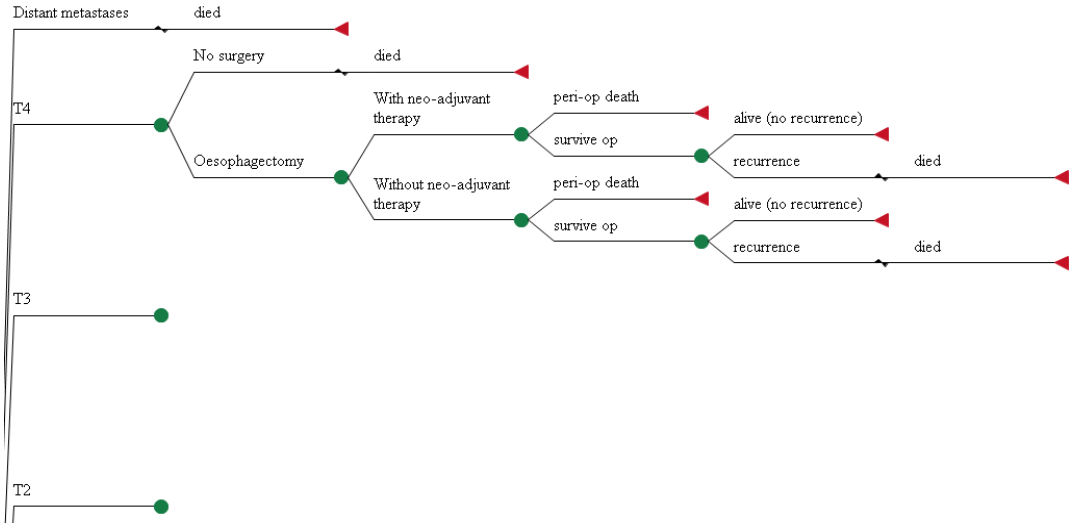
Figure 1b Illustration of decision analytic model for T2-Distant Metastases



NB: Branches T2 and T3 are identical to T4.

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